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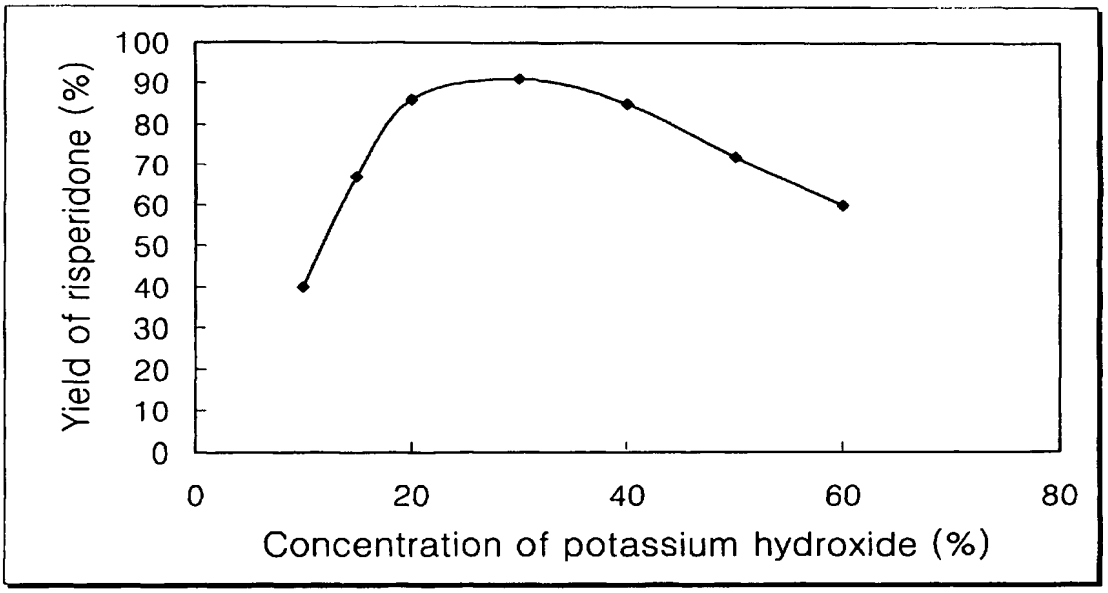
(54) Title: METHOD FOR PREPARING RISPERIDONE



(57) Abstract: Risperidone is prepared in a high yield by reacting 2,4-difluorophenyl(4-piperidinyl)methanone oxime hydrochloride and 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one in an aqueous alkali hydroxide solution having an alkali hydroxide concentration in the range of 20 to 40%.

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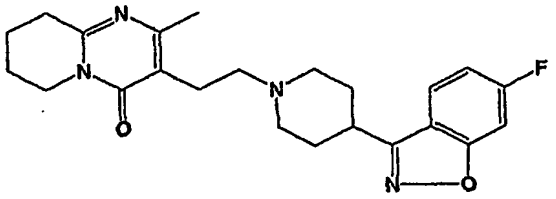
METHOD FOR PREPARING RISPERIDONE

FIELD OF THE INVENTION

The present invention relates to an improved method for preparing risperidone.

BACKGROUND OF THE INVENTION

Risperidone, which is the generic name for the compound of formula (I), 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, is a potent antipsychotic agent, especially useful for treating schizophrenia:

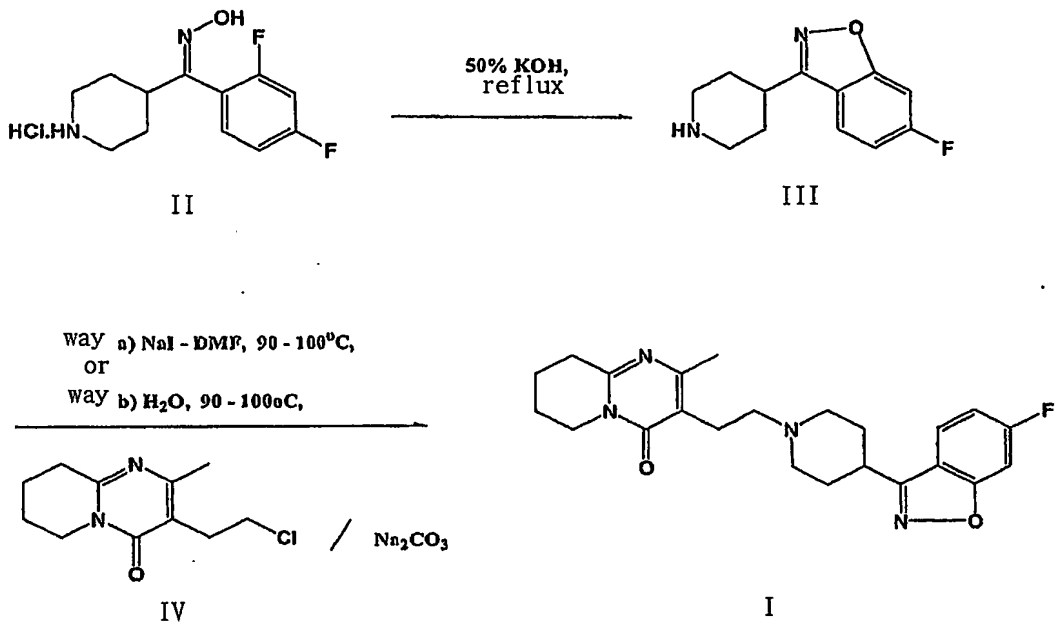


(I)

There have been reported a number of methods for risperidone synthesis but these methods generally suffer from the problems of low yield and complicated procedures.

For example, the benzisoxazol derivative of formula (III) obtained by ring closure of the oxime derivative of formula (II) is coupled with the pyrimidine derivative of formula (IV) to give risperidone, as shown in Scheme 1.

Scheme 1

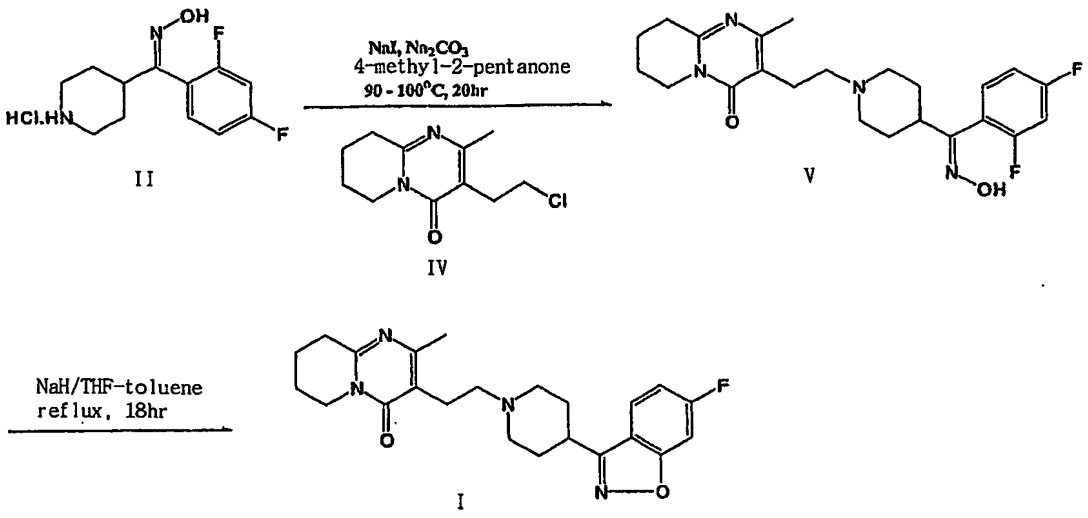


In Scheme 1, the coupling reaction of the benzisoxazol derivative (III) and the pyrimidine derivative (IV) may be performed by the method disclosed in U.S. Patent No. 4,804,663, wherein the coupling reaction is performed in N,N-dimethylformamide in the presence of a sodium iodide catalyst (way a). However, this method gives a low yield of about 46% (overall yield of about 35%) due to the occurrence of side reactions such as self-polymerization of the benzisoxazol derivative (III).

Alternatively, the coupling reaction may be carried out using the method, International Publication No. WO 01/85731 which uses water as solvent instead of N,N-dimethylformamide so as to suppress the side reactions (way b). However, this method also gives an overall yield of only 55%.

Korean Patent Publication No. 96-9435, on the other hand, discloses a method as illustrated in Scheme 2, wherein the compound of formula (V) obtained by coupling of the oxime derivative of formula (II) with the pyrimidine derivative of formula (IV) is subjected to ring closure in the presence of a strong base such as sodium hydride.

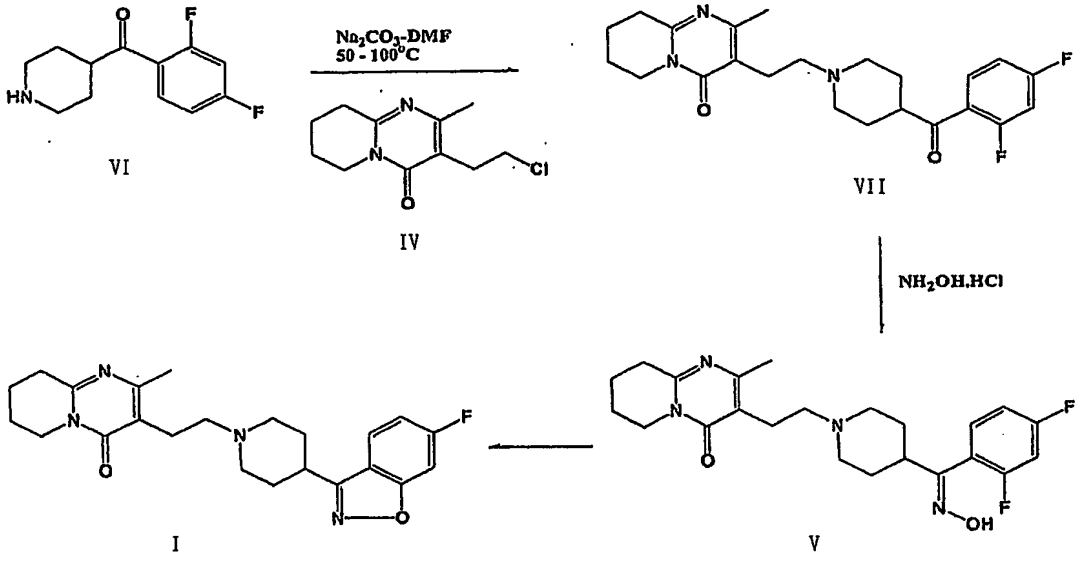
Scheme 2



However, this method still has a problem in that the overall yield is only 45%. In addition, this method has to deal with the risk of sodium hydride explosion.

Further, Spanish Patent No. 2,050,069 discloses a method for preparing risperidone which is described in Scheme 3: the compound of formula (VII) obtained by coupling of the benzoylpiperidine derivative of formula (VI) and the pyrimidine derivative of formula (IV) is subjected to oximation to give the compound (V), and ring closure thereof gives risperidone.

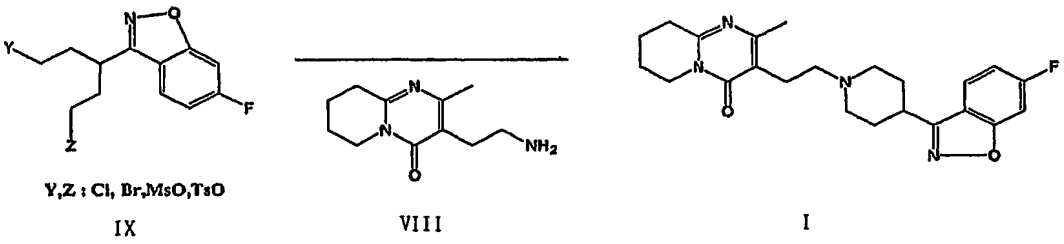
Scheme 3



This method also gives a low coupling yield of 63%, and complicated work-up procedures are required.

Spanish Patent No. 2,074,966 describes a method of preparing risperidone as presented in Scheme 4, wherein the risperidone of formula (I) is obtained by the reaction of the oxazol derivative of formula (IX) and the aminopyridin derivative of formula (VIII).

Scheme 4

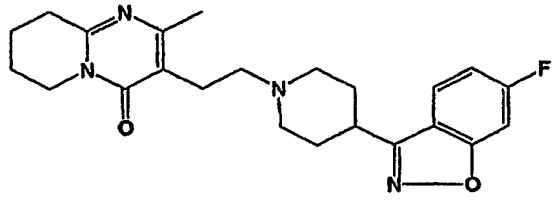


However, this method is hampered by the problem that the processes of preparing the starting materials of formula (VIII) and (IX) are complicated.

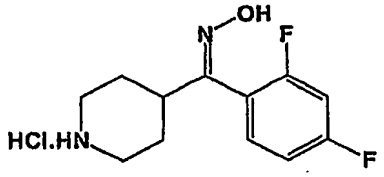
SUMMARY OF THE INVENTION

Accordingly, it is an object of the present invention to provide a simple, improved method of preparing risperidone in a high yield.

In accordance with one aspect of the present invention, there is provided a method of preparing risperidone of formula (I) which comprises reacting the oxime derivative of formula (II) and a haloethylpyrimidine derivative of formula (X) in an aqueous alkali solution:



(I)



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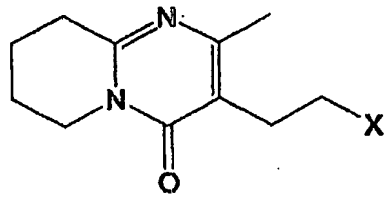


(X)

wherein, X is a halogen.

BRIEF DESCRIPTION OF THE DRAWINGS

The above and other objects and features of the present invention will become apparent from the following description of the invention, when taken in conjunction with the accompanying drawing, in which:

Fig. 1 shows the change in the yield of risperidone (%) with the

concentration of potassium hydroxide (%), as observed in Reference Example.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is characterized by accomplishing the coupling reaction and the ring closure reaction in one step by way of using selected reactants in an aqueous alkali solution having an alkali hydroxide concentration in the range of 20 to 40%.

According to the present invention, the oxime derivative of formula (II), 2,4-difluorophenyl (4-piperidinyl) methanone oxime hydrochloride, and the haloethylpyrimidine derivative of formula (X), 3-(2-haloethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one, are used as starting materials, which are commercially available or may be prepared in accordance with the methods described in U.S. Patent Nos. 4,485,107 and 4,804,663.

In a preferred embodiment, the haloethylpyrimidine derivative of formula (X) may be employed in an amount ranging from 1.0 to 2.0 equivalents, preferably 1.1 to 1.3 equivalents, based on the amount of the oxime derivative of formula (II).

In a preferred embodiment, the concentration of the aqueous alkali solution used in the present invention is in the range of 20 to 40%, preferably 30%. If the concentration of the aqueous alkali solution is less than 20%, the yield decreases due to the generation of excessive by-products. On the other hand, if the concentration of the aqueous alkali solution is more than 40%, the yield is decreased due to the increase of decomposed products.

Representative examples of the alkali hydroxide include sodium hydroxide, potassium hydroxide, lithium hydroxide and a mixture thereof, more preferably potassium hydroxide.

In a preferred embodiment, the aqueous alkali solution may be employed in an amount ranging from 5 to 15 ml, preferably 7 to 11 ml based on 1g of the oxime derivative of formula (II).

In a preferred embodiment, the inventive reaction may be conducted at a

temperature in the range of 100 to 140℃, preferably 100 to 130℃ for 1 to 6 hours, preferably, 1.5 to 3 hours.

In accordance with the present invention, risperidone can be obtained in a much higher yield of at least 80% than previously possible. Further, according to the present invention, the conventional coupling and the ring closure reactions, which comprise several cumbersome steps can be performed simultaneously in one step. In addition, risperidone obtained in the present invention may be refined to a purity of 99.5% or more, by a simple recrystallization procedure.

The following Examples are intended to further illustrate the present invention without limiting its scope.

Further, percentages given below for solid in solid mixture, liquid in liquid, and solid in liquid are on a wt/wt, vol/vol and wt/vol basis, respectively, and all the reactions were carried out at room temperature, unless specifically indicated otherwise.

Preparation Example 1: Preparation of 2,4-difluorophenyl(4-piperidinyl)methanone oxime hydrochloride (the compound of formula II)

A) Preparation of 1-acetyl-4-(2,4-difluorobenzoyl)piperidine

67g of 1,3-difluorobenzene and 133g of ammonium chloride were added to 150ml of dichloromethane, and then the mixture was cooled to room temperature. 98g of 1-acetyl-4-piperidinecarbonyl chloride in 50ml of dichloromethane was added thereto dropwise, and then the mixture was stirred at an elevated temperature for 3 hours. The reaction mixture was poured to a mixture of ice and hydrochloric acid, and the resulting mixture was extracted with 200ml of dichloromethane. The organic phase was separated, dried over anhydrous magnesium sulfate, filtered, and the solvent was removed from the filtrate to obtain 55.9g of the title compound (yield: 41%).

B) Preparation of 2,4-difluorophenyl(4-piperidinyl)methanone hydrochloride

56g of 1-acetyl-4-(2,4-difluorobenzoyl)piperidine obtained in step A) was added to 190ml of 6N hydrochloric acid, and then, the resulting mixture was refluxed for 5 hours. The reaction mixture was concentrated under a reduced pressure, 200ml of 2-propanol was added to the residue, and then the mixture was stirred. The resulting solid was filtered and dried to obtain 46.6g of the title compound (yield: 85%).

C) Preparation of 2,4-difluorophenyl(4-piperidinyl)methanone oxime hydrochloride

30g of 2,4-difluorophenyl(4-piperidinyl)methanone hydrochloride obtained in step B) and 30g of hydroxylamine hydrochloride were added to 50ml of ethanol. 29.5ml of N,N-dimethylethanolamine was added thereto dropwise while stirring at room temperature, and then the mixture was refluxed for 3 hours. The reaction mixture was cooled to room temperature, and the precipitated solid was filtered and dried to obtain 26.4g of the title compound as a white crystal (yield: 96%).

Preparation Example 2: Preparation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (compound of formula X)

A) Preparation of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

40g of 2-aminopyridine and 75ml of 3-acetyl-4,5-dihydro-2(3H)-furanone were added to 1.0L of toluene, and then 200ml of phosphorus oxychloride was added thereto dropwise over 1 hour. The resulting mixture was slowly heated and refluxed for 5 hours. The reaction mixture was concentrated under a reduced pressure and the residue was poured to a mixture of ice and ammonia water. The resulting solid was extracted with 1.0L of dichloromethane, dried and filtered. The filtrate was concentrated under a reduced pressure to remove dichloromethane and 500ml of isopropanol was added to the residue. The resulting crystal was

filtered, washed and dried to obtain 48.1g of the title compound as a off-white crystal (yield: 52%).

B) Preparation of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one

28g of 3-(2-chloroethyl)-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one obtained in step A) was dissolved in 90ml of 6N hydrochloric acid, 2.8g of 10%-palladium was added thereto, and then the mixture was hydrogenated under a hydrogen pressure of 35psi at room temperature for 8 hours. The reaction mixture was filtered through Cellite and the filtrate was concentrated under a reduced pressure, 200ml of isopropanol was added to the residue, and then the mixture was stirred. The solid was filtered and dried to obtain 25.1g of the title compound as a white crystal (yield: 90%).

Example 1: Preparation of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (risperidone)

2.77g of 2,4-difluorophenyl(4-piperidinyl)methanone oxime hydrochloride obtained in Preparation Example 1 and 2.26g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one obtained in Preparation Example 2 were added to 27ml of 30% aqueous potassium hydroxide, and then the resulting mixture was stirred at 120 to 130℃ for 90 minutes. The reaction mixture was cooled to room temperature, filtered, and the obtained solid was added to 16ml of N,N-dimethylformamide. The resulting suspension was heated to 80℃, left at that temperature for 5 minutes, and then slowly cooled to room temperature. The resulting crystal was filtered, washed with 5ml of water and dried to obtain 3.39g of the title compound as a white crystal (yield: 82%).

Melting point: 167~169℃;

Purity: 99.7% (by HPLC);

^{1}H-NMR (300㎒, $CDCl_3$): δ 7.65-7.61 (m, 1H), 7.18-7.14 (m, 1H), 7.00-6.94 (m, 1H), 3.87-3.83 (m, 2H), 3.12-3.07 (m, 2H), 2.97-3.02 (m, 1H), 2.81-2.76 (m, 2H), 2.71-2.66 (m, 2H), 2.48-2.43 (m, 2H), 2.23 (s, 3H), 2.34-2.19 (m, 2H), 2.05-2.01 (m, 4H), 1.87-1.79 (m, 4H).

Example 2: Preparation of 3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one (risperidone)

The procedure of Example 1 was repeated except that 40% aqueous potassium hydroxide was used to obtain 3.27g of the title compound as a white crystal (yield: 80%).

Purity: 99.5% (by HPLC);

Melting point and ^{1}H-NMR data were the same as in Example 1.

Comparative Example: Preparation of risperidone in accordance with International Publication No. WO 01/85731

A) Preparation of 4-(6-fluoro-1,2-benzisoxazol-3-yl)-piperidine (the compound of Formula III)

5.52g of 2,4-difluorophenyl(4-piperidinyl)methanone oxime hydrochloride obtained in Preparation Example 1 was added to 25ml of 50% potassium hydroxide, and then the mixture was refluxed for 4 hours. Subsequently, the reaction mixture was cooled to room temperature, extracted twice with 25ml portions of toluene. The combined organic phase was dried over anhydrous magnesium sulfate, filtered, and the filtrate was concentrated under a reduced pressure. The resulting solid was recrystallized from 20ml of ether, to obtain 3.29g of the title compound (yield: 75%).

^{1}H-NMR (300㎒, $CDCl_3$): δ 7.67-7.71 (m, 1H), 7.22-7.26 (m, 1H), 6.97-7.09 (m, 1H), 3.16-3.27 (m, 3H), 1.92-2.08 (m, 4H).

B) Preparation of risperidone

2.27g of 4-(6-fluoro-1,2-benzisoxazol-3-yl)-piperidine obtained in step A) and 2.26g of 3-(2-chloroethyl)-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,2-a]pyrimidin-4-one obtained in Preparation Example 2 were added to a solution of 2.25g of Na_2CO_3 in 12ml of water. The resulting mixture was stirred at 85 to 90℃ for 4 hours, cooled to room temperature, and filtered. The resulting solid was added to 16ml of N,N- dimethylformamide. The resulting suspension was heated to 80℃, left at that temperature for 5 minutes, and then slowly cooled to room temperature. The crystal was filtered, washed with 5ml of water and dried to obtain 3.02g of the title compound as a white crystal (yield: 73%).

The melting point and ^{1}H-NMR data were the same as in Example 1.

Reference Example: Change of the yield of risperidone (%) depending on the concentration of potassium hydroxide (%)

The procedure of Example 1 was repeated using 10, 15, 20, 30, 40, 50 or 60% aqueous potassium hydroxide and the yield of risperidone (by HPLC) was examined. The results are shown in Table 1 and Figure 1.

Table 1

Concentration of potassium hydroxide (%)	10	15	20	30	40	50	60
Yield of risperidone (%)	40	67	86	91	85	72	60

As shown in Table 1 and Figure 1, the yield of risperidone varies with the

concentration of potassium hydroxide. The use of a potassium hydroxide concentration in the range of 20 to 40% provides risperidone at a good yield of at least 80%.

For reference, the comparison of the yields of risperidone according to the present invention and prior arts methods are shown in Table 2, for the purpose of verification of the effects of the present invention.

Table 2

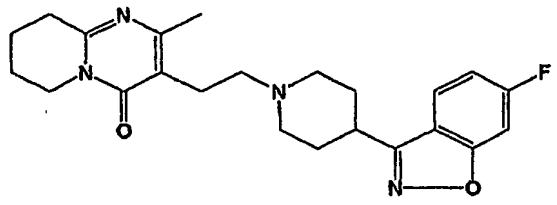
	Yield (%)		
	Coupling reaction	Ring closure reaction	Overall reaction
U.S. Patent No. 4,804,663	46	76	35
International Publication No. WO 01/85731	72	76	55
Korean Patent No. 96-9435	77	58	45
Spanish Patent No. 2,050,069	63	85	54
Present invention	performed simultaneously by one step		no less than 80

As shown in Table 2, the method of the present invention is capable of providing risperidone in a markedly higher yield than any of the conventional methods.

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

WHAT IS CLAIMED IS:

1. A method of preparing risperidone of formula (I) which comprises reacting the oxime derivative of formula (II) and a haloethylpyrimidine derivative of formula (X) in an aqueous alkali hydroxide solution having an alkali hydroxide concentration in the range of 20 to 40%:



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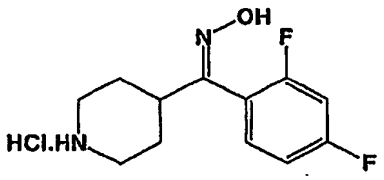
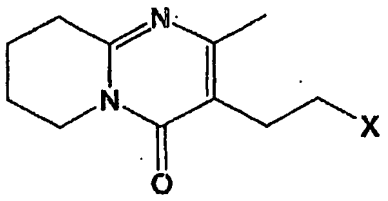


(II)



(X)

wherein, X is a halogen.

2. The method of claim 1, wherein the alkali hydroxide is selected from the group consisting of sodium hydroxide, potassium hydroxide, lithium hydroxide and a mixture thereof.

3. The method of claim 2, wherein the alkali hydroxide is potassium hydroxide .

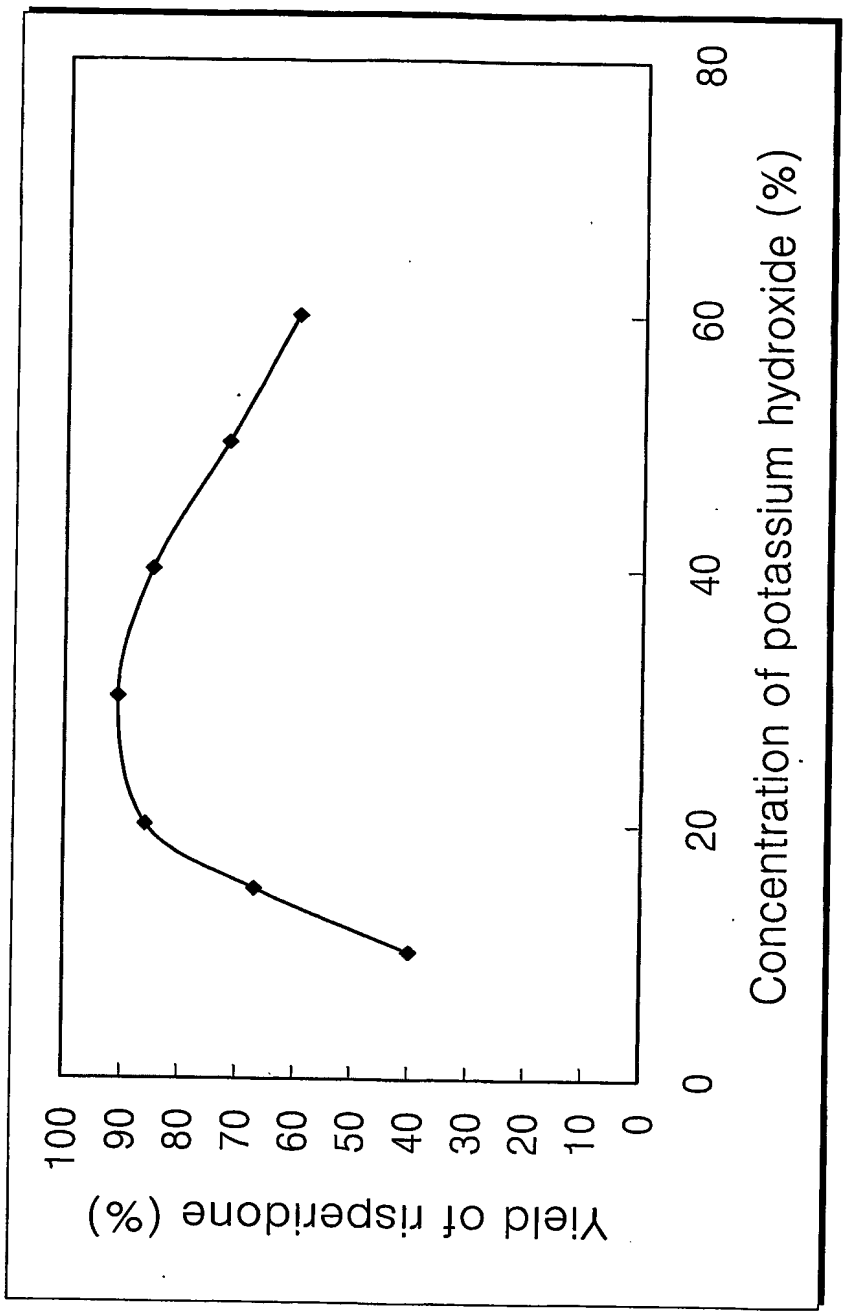
4. The method of claim 1, wherein the aqueous alkali solution is employed

in an amount ranging from 5 to 15 ml based on 1g of the oxime derivative of formula (II).

5. The method of claim 1, wherein the haloethylpyrimidine derivative of formula (X) is employed in an amount ranging from 1.0 to 2.0 equivalents based on the amount of the oxime derivative of formula (II).

6. The method of claim 1, wherein the reaction is conducted at a temperature in the range of 100 to 140℃.

FIG. 1


Yield of risperidone (%)
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
Concentration of potassium hydroxide (%)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR2003/002171

A. CLASSIFICATION OF SUBJECT MATTER

IPC7 C07D 413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 07 C07D, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean Patents and Application for Inventions since 1975

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS online (STN), Medline, Delphion

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ES 2050069 A1 (Vita-Invest, S.A.) 01.May 1994 See whole document	1-6
A	EP 0196132 A2 (Janssen Pharmaceutica N.V.) 01.Oct.1986 See whole document	1-6
A	WO 0212200 A1 (Teva Pharmaceuticals) 14.Feb.2002 See whole document	1-6
A	WO0185731 A1 (RPG Life Sciences Ltd.) 05.May 2000 See whole document	1-6

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
09 JANUARY 2004 (09.01.2004)	10 JANUARY 2004 (10.01.2004)

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Authorized officer
SIHN, YOUNG SIHN
Telephone No. 82-42-481-8162

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR2003/002171

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
ES2050069A1	01.05.1994	None	
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